# CORRESPONDENCE

## Re: Plasma Sex Steroid Hormone Levels and Risk of Breast Cancer in Postmenopausal Women

Sex steroid hormone concentrations in serum (or plasma) have been positively related to postmenopausal breast cancer in several cohorts. Most recently, Hankinson et al. *(1)* reported in the Journal that postmenopausal women in the Nurses' Health Study with elevated levels of plasma estradiol, testosterone, and dehydroepiandrosterone (DHEA) sulfate were at a significantly increased risk when the relationship of each hormone to breast cancer was analyzed separately. However, when estradiol was included in statistical models, risk estimates for testosterone were substantially attenuated and no longer statistically significant, whereas risk estimates for DHEA sulfate and estradiol were reduced only modestly. The authors concluded that plasma estradiol is probably causally related to breast cancer risk in postmenopausal women, whereas testosterone is more likely to be indirectly related to risk through its conversion to estradiol. Potential mechanisms of action for DHEA sulfate were explored.

We previously reported *(2,3)* an increased risk of breast cancer among postmenopausal women in the Columbia, MO, Breast Cancer Serum Bank cohort with elevated serum levels of non-sex hormone-binding globulin (SHBG)-bound estradiol, testosterone, and DHEA. We did not, however, control for estradiol when evaluating relationships of androgens with risk. Our study included 71 case subjects with two control subjects per case subject matched on age and on date and time of day of blood collection. All participants were postmenopausal women who were free of cancer and not taking exogenous estrogens when they donated blood to the serum bank. The median age of the participants at blood collection was 62 years, and the time from blood collection to diagnosis ranged from less than 1 year to 9.5 years. Written informed consent was obtained from all participants.

**Table 1.** Relative risks (RRs) (95% confidence intervals [CI]) for breast cancer by quartile of serum hormone concentrations*

| | RR (95% CI) by serum hormone level quartile categories† | | | | *P* for trend‡ |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | |
| Model 1 | | | | | |
| Non-SHBG-bound estradiol | 1.0 (referent) | 5.9 (1.8–19.3) | 4.8 (1.5–15.7) | 5.2 (1.5–18.5) | .12 |
| Model 2 | | | | | |
| Testosterone | 1.0 (referent) | 2.9 (0.9–9.4) | 2.9 (1.0–8.6) | 6.2 (2.0–19.0) | .002 |
| Model 3 | | | | | |
| DHEA | 1.0 (referent) | 1.8 (0.6–5.3) | 2.9 (1.0–8.2) | 4.0 (1.3–11.8) | .02 |
| Model 4 | | | | | |
| Non-SHBG-bound estradiol | 1.0 (referent) | 5.1 (1.3–19.2) | 3.4 (0.9–12.3) | 3.4 (0.8–14.3) | .68 |
| Testosterone | 1.0 (referent) | 2.0 (0.6–7.6) | 2.1 (0.6–7.3) | 4.6 (1.3–16.6) | .01 |
| DHEA | 1.0 (referent) | 1.4 (0.4–4.9) | 1.5 (0.4–4.7) | 1.5 (0.4–5.3) | .31 |

*RRs were calculated by use of conditional logistic regression and adjusted for time since menopause, height, weight, parity, and family history of breast cancer.

†Quartile cut points were less than 3.1, 3.2–6.0, 6.1–10.5, and 10.6 or more pg/mL for non-sex hormone-binding globulin (SHBG)-bound estradiol, less than 0.10, 0.11–0.17, 0.18–0.26, and 0.27 or more ng/mL for testosterone, and less than 0.92, 0.93–1.61, 1.62–2.58, and 2.59 or more ng/mL for dehydroepiandrosterone (DHEA).

‡*P* value (two-sided) for trend is from a model with log-transformed hormone concentration included as a continuous variable.

Serum concentrations of non-SHBG-bound estradiol, testosterone, and DHEA were significantly correlated (Spearman $r$ = .29–.38). Relative risks (RRs) associated with these hormones both with and without mutual adjustment are summarized in Table 1. When all were included in a single model, the apparent association with breast cancer was attenuated slightly and similarly for estradiol and testosterone but more so for DHEA (e.g., 43%, 31%, and 83% reductions in the excess RR for the top quartiles of estradiol, testosterone, and DHEA, respectively).

Thus, within the limitations of our sample size, estradiol, testosterone, and possibly DHEA appeared to have independent positive effects on breast cancer risk. These results are similar to those from the ORDET (hormones and diet in the etiology of breast tumors) study *(4)*, where mutual adjustment resulted in persistence of a testosterone effect but weakening of estradiol and DHEA sulfate effects. On the other hand, a result for testosterone similar to that of Hankinson et al. *(1)* was found in another cohort study *(5)*. Differences between these studies in the specific analytes associated with risk, in the strength and consistency of the associations, and in the underlying distributions of hormone concentrations could contribute to differing results, as could the inherent difficulty in disentangling the effects of correlated variables. What is clear from these recent cohort studies, as well as from a number of case–control investigations, is that androgens are consistently found to be related to breast cancer risk. Clarification of the underlying mechanism(s) for this observation (via estrogenic and/or independent pathways) could substantially increase our understanding of the specific hormonal basis of this disease.

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## NOTES

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## Re: Quality of Life in Advanced Prostate Cancer: Results of a Randomized Therapeutic Trial

A link between the pharmacology of flutamide and the quality of life (QOL) of patients with metastatic prostate cancer was recently reported *(1)*. In the National Cancer Institute/Southwest Oncology Group INT-0105 trial, better QOL scores were reported in patients receiving orchiectomy plus placebo than in patients receiving orchiectomy plus flutamide. Subjective assessments need, however, to be interpreted in the light of possible confounders of either the causes or the effects. One confounder was discussed—imbalance favoring placebo *(1)*—but several others need to be explored systematically.

A combined treatment was evaluated (orchiectomy plus flutamide); therefore, any difference observed with orchiectomy can be explained by either flutamide or an interaction between flutamide and orchiectomy. Orchiectomy has a rapid effect on testosterone levels, and it increases cortisol secretion in response to stress *(2)*. The symptoms observed are the result of the addition of flutamide to a situation already producing a rapid androgen deprivation with additional hormonal changes, all occurring to a lesser extent with luteinizing hormone-releasing hormone. This did not translate, however, into a decrease of mental and physical scores, as compared with baseline.

In a randomized, controlled trial, the patients know that they can receive a treatment or a placebo. Their expectations of treatment effects are set, by this uncertainty, between the expected effects of the treatment and the expected effects of no treatment. Expectations are known to influence subjective assessments *(3)*. The subjective assessments of the benefit are underestimated in the treatment arm and overestimated in the placebo arm. This situation minimizes the differences between treatment arms, and a subgroup of patients with side effects may then become the major determinant of how QOL scores compare.

Pain medications and antidepressants represent outcomes of QOL studies. The prostate-specific antigen (PSA) level was decreased more with flutamide than with placebo *(4)*. In such a situation, one may expect less symptomatic medications to be prescribed. These medications can change QOL scores and should be reported.

Withdrawals represent another outcome of QOL studies. In the INT-0105 trial, more withdrawals were observed in the placebo arm. The number of patients returning questionnaires was slightly different at baseline between flutamide and placebo (370 and 367 patients, respectively). The difference increased after 6 months for outcomes such as frequent pain (19 more patients in the flutamide arm), intense pain (18 more patients in the flutamide arm), mental health (17 more patients in the flutamide arm), and distress (16 more patients in the flutamide arm). The status of the missing patients can have an impact on the QOL scores.

A recent publication described symptoms of anxiety and depression in patients with prostate cancer *(5)* and suggested the use of a questionnaire to detect patients with psychiatric needs. For these patients, flutamide may temporally or definitely be withdrawn. The risk of side effects should, however, be balanced with long-term benefits. A survival advantage of 9% was reported *(4)*, but it may have underestimated the true benefit of flutamide because the model used was not adjusted for prognostic factors. Unadjusted models sometimes underestimate the treatment effects *(6)* and have a lower predictive value for the individual patient than multivariate models. The benefits of orchiectomy should also be compared with the benefits of luteinizing hormone-releasing hormone, in terms of QOL, risk of osteoporosis, and survival *(7)*.

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## NOTE

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## RESPONSE

Dr. Caubet first notes that the treatment arms in the quality-of-life (QOL) sample were not balanced with respect to extent of disease. In the article, we reported this, but we also noted that extent of disease was included in all longitudinal analyses and did not change our conclusions.

Dr. Caubet is correct in noting that average scores for physical and emotional functioning did not worsen significantly over the 6-month assessment period for either arm. However, we did report that the emotional functioning of patients receiving orchiectomy plus placebo improved more over this 6-month period than did that of patients receiving